

CLINICAL PRACTICE

Celiac Disease

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 22-year-old woman fractures her wrist while playing volleyball. She reports a history of fatigue and intermittent oral ulcerations but no other symptoms. Radiography of her wrist shows osteopenia. Laboratory testing is notable for a hematocrit of 32% and low levels of ferritin and 25-hydroxyvitamin D. Although she reports no gastrointestinal symptoms, celiac disease is suspected. How should she be further evaluated and, if testing indicates celiac disease, how should her case be managed?

THE CLINICAL PROBLEM

Celiac disease is a systemic immune-mediated disorder triggered by dietary gluten in genetically susceptible persons. Gluten is a protein complex found in wheat, rye, and barley. Celiac disease is characterized by a broad range of clinical presentations, a specific serum autoantibody response, and variable damage to the small-intestinal mucosa.¹

Celiac disease affects 0.6 to 1.0% of the population worldwide,^{2,3} with wide regional differences in Europe (e.g., the prevalence is 0.3% in Germany and 2.4% in Finland) for reasons that are unclear.⁴ Celiac disease is also common in developing countries, particularly in North Africa⁵ and the Middle East.⁶ In India, celiac disease is observed mainly in the northwestern part of the country, where wheat is a staple food.⁷ Cases of celiac disease also have been described in China.⁸ The frequency of celiac disease is increasing in many developing countries because of westernization of the diet, changes in wheat production and preparation, increased awareness of the disease, or a combination of these factors.

Serologic screening studies have shown that only a small proportion of cases of celiac disease are clinically recognized (21% in a recent European study).⁴ The prevalence is 1.5 to 2 times as high among women as among men and is increased among persons who have an affected first-degree relative (10 to 15%), type 1 diabetes (3 to 16%), Hashimoto's thyroiditis (5%) or other autoimmune diseases (including autoimmune liver diseases, Sjögren's syndrome, and IgA nephropathy), Down's syndrome (5%), Turner's syndrome (3%), and IgA deficiency (9%).⁹⁻¹⁴

Genetic background plays a key role in the predisposition to the disease. The HLA-DQ2 haplotype (DQA1*0501/DQB1*0201) is expressed in the majority of patients with celiac disease (90%), whereas it is expressed in one third of the general population. In another 5% of patients with celiac disease, the HLA-DQ8 haplotype (DQA1*0301/DQB1*0302) is expressed, whereas almost all the remaining 5% of patients have at least one of the two genes encoding DQ2 (DQB1*0201 or DQA1*0501). DQ2 and DQ8 haplotypes expressed on the surface of antigen-presenting cells can bind activated (deamidated) gluten peptides, triggering an abnormal immune re-

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KEY CLINICAL POINTS

CELIAC DISEASE

- Once considered a gastrointestinal disorder that mainly affects white children, celiac disease is now known to affect persons of different ages, races, and ethnic groups, and it may be manifested without any gastrointestinal symptoms.
- Measurement of IgA anti–tissue transglutaminase antibodies is the preferred initial screening test for celiac disease because of its high sensitivity and specificity, but it performs poorly in patients with IgA deficiency (which is more common in patients with celiac disease than in the general population).
- The diagnosis is confirmed by means of upper endoscopy with duodenal biopsy, although recent guidelines suggest that biopsy may not be necessary in selected children with strong clinical and serologic evidence of celiac disease.
- Given the undisputable role of gluten in causing celiac disease enteropathy, the cornerstone of treatment is the implementation of a strict gluten-free diet for life.
- Gluten sensitivity may occur in the absence of celiac disease, and a definitive diagnosis should be made before implementing a lifelong gluten-free diet.

sponse. The DQ2 and DQ8 haplotypes are necessary but not sufficient for the development of celiac disease.¹⁵ So far, at least 39 non-HLA genes that confer a predisposition to the disease have been identified, most of which are involved in inflammatory and immune responses.¹⁶

The pathogenesis of celiac disease involves an external trigger (gluten), changes in intestinal permeability, enzymatically modified gluten, HLA recognition, and innate and adaptive immune responses to gluten peptides involving self-antigens (e.g., transglutaminase), eventually leading to celiac enteropathy.^{17,18} Since gluten is pivotal in triggering this chain of events, a gluten-free diet is the cornerstone therapy for celiac disease.

CLINICAL PRESENTATION

Once considered a gastrointestinal disease of childhood affecting mainly whites, celiac disease is now recognized as a systemic disease that may affect persons of any age and many races and ethnic groups. The clinical features of celiac disease are protean and reflect its systemic nature. Frequent symptoms and signs include chronic diarrhea, weight loss, and abdominal distention (in 40 to 50% of patients). Other manifestations include iron deficiency with or without anemia, recurrent abdominal pain, aphthous stomatitis, short stature, high aminotransferase levels, chronic fatigue, and reduced bone mineral density.¹ Unusual manifestations of celiac disease include dermatitis herpetiformis, a blistering rash with pathognomonic cutaneous IgA depos-

its¹⁹; gluten ataxia, a sporadic form of ataxia with positive serologic markers for gluten sensitization (although the association with celiac disease is still debated)²⁰; and celiac crisis, a rare life-threatening syndrome, mostly observed in children, that is characterized by severe diarrhea, hypoproteinemia, and metabolic and electrolyte imbalances. Clinically silent celiac disease has been increasingly detected by means of serologic screening.

Complications associated with untreated celiac disease include osteoporosis, impaired splenic function, neurologic disorders, infertility or recurrent abortion, ulcerative jejunoileitis, and cancer.²¹ Enteropathy-associated T-cell lymphoma and adenocarcinoma of the jejunum are rare complications of celiac disease.²²

Refractory celiac disease is diagnosed when there are persistent or recurrent malabsorptive symptoms and signs with villous atrophy detected on biopsy despite maintenance of a strict gluten-free diet for more than 12 months. Refractory celiac disease can be classified as type 1 (normal intraepithelial lymphocytes) or type 2 (abnormal intraepithelial lymphocytes; clonal intraepithelial lymphocytes lacking surface markers CD3, CD8, and T-cell receptors; or both). Type 2 is associated with a higher risk of ulcerative jejunoileitis and lymphoma than type 1.²³

NATURAL HISTORY

The natural history of celiac disease varies widely among patients. Longitudinal data suggest the following sequence of events: the appearance of

Table 1. Serum Tests for the Diagnosis of Celiac Disease.*

Test	Sensitivity (Range)	Specificity (Range)	Comments
	<i>percent</i>		
IgA anti-tTG antibodies	>95.0 (73.9–100)	>95.0 (77.8–100)	Recommended as first-level screening test
IgG anti-tTG antibodies	Widely variable (12.6–99.3)	Widely variable (86.3–100)	Useful in patients with IgA deficiency
IgA antiendomysial antibodies	>90.0 (82.6–100)	98.2 (94.7–100)	Useful in patients with an uncertain diagnosis
IgG DGP	>90.0 (80.1–98.6)	>90.0 (86.0–96.9)	Useful in patients with IgA deficiency and young children
HLA-DQ2 or HLA-DQ8	91.0 (82.6–97.0)	54.0 (12.0–68.0)	High negative predictive value

* Data are from Husby et al.²⁸ and Giersiepen et al.²⁹ DGP denotes deamidated gliadin peptides, and tTG tissue transglutaminase.

“celiac” antibodies, the development of intestinal enteropathy, the onset of symptoms, and the development of complications. Not all of these events may occur. The duration of each phase may range from weeks to decades. Potential celiac disease is characterized by the presence of celiac autoantibodies in the serum in patients with a normal intestinal mucosa on biopsy. Overt intestinal damage develops over time in a subgroup of these patients.²⁴

In contrast to the previous theory that immunologic and mucosal changes typically develop early in life (soon after exposure to gluten at weaning), more recent long-term studies indicate that seroconversion to celiac autoimmunity may occur at any time.²⁵ This observation suggests that genetic susceptibility and ingestion of gluten-containing grains are necessary but not sufficient conditions for the loss of gluten tolerance and the development of celiac disease.

Loss of gluten tolerance appears to be reversible in some patients. In a Finnish follow-up study, 49% of children genetically at risk for celiac disease had seroconversion from positive tests for IgA anti-tissue transglutaminase antibodies to negative tests, despite continued exposure to gluten.²⁶ Case reports have described adults with documented celiac disease in childhood who later reintroduced gluten into their diets but continued to have negative serologic tests and normal villous architecture.²⁷ Patients with serologic findings that revert to negative titers should still be followed, since serologic status (and intestinal damage) may vary over time.

STRATEGIES AND EVIDENCE

DIAGNOSIS

Serologic tests are fundamental for celiac disease screening (Table 1). Serologic screening is also recommended in all first-degree family members of patients who receive a diagnosis of celiac disease. Measurement of serum IgA anti-tissue transglutaminase antibodies is recommended for initial testing in persons who do not have concomitant IgA deficiency because of its high sensitivity (94%), high specificity (97%), and excellent standardization³⁰; IgG anti-tissue transglutaminase antibodies can be measured in persons with IgA deficiency. Point-of-care tests assessing anti-tissue transglutaminase antibodies in a drop of whole blood have been developed,³¹ but they are not recommended for diagnosis because of possible false negative results.⁵ Measurement of IgA anti-endomysial antibodies is nearly 100% specific for active celiac disease,²⁹ but it should be used only as a confirmatory test in the case of borderline positive or possibly false positive results of tests for anti-tissue transglutaminase antibodies, as occurs in other autoimmune diseases, including type 1 diabetes. Tests for IgA anti-endomysial antibodies are also expensive and operator-dependent. Measurement of deamidated gliadin peptide antibodies of the IgG class, which has recently been introduced as an alternative test, is reported to have better sensitivity and specificity than measurement of IgG anti-tissue transglutaminase antibodies as a screening test for celiac disease in IgA-deficient patients.³² The sensitivity

of serologic testing is markedly reduced in patients with a gluten-restricted diet; patients should therefore not restrict their diet before testing.

A biopsy of the small intestine is required to confirm the diagnosis in most patients with suspected celiac disease. The characteristic histologic changes include an increased number of intraepithelial lymphocytes (>25 per 100 enterocytes), elongation of the crypts, and partial to total villous atrophy.¹ However, false positive results (e.g., normal mucosa with an atrophic appearance in a specimen that has not been cut longitudinally) and false negative results (owing to patchiness of the mucosal damage) may occur. The detection of subepithelial anti-tissue transglutaminase antibody IgA deposits by means of double immunofluorescence may be useful in patients with an uncertain diagnosis, such as patients with negative serologic results and positive results on biopsy.³³ Recent guidelines from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition suggest that a biopsy of the small intestine may not be required in children with typical symptoms, a high titer of anti-tissue transglutaminase antibodies (higher than 10 times the upper limit of the normal range), and predisposing HLA genotypes.²⁸

Testing for HLA-DQ2 and HLA-DQ8 may be useful in at-risk persons (e.g., family members of patients with celiac disease). Such testing has a high negative predictive value, which means that the disease is very unlikely to develop in persons who are negative for both HLA-DQ2 and HLA-DQ8.¹⁵

Specific diagnostic procedures such as double-balloon enteroscopy (an endoscopic procedure for examining the entire small intestine), capsule endoscopy, and magnetic resonance imaging are infrequently warranted but may be helpful in complicated cases.

TREATMENT

Treatment of celiac disease involves a gluten-free diet (i.e., a diet with no wheat, rye, or barley proteins). A wide range of gluten-free wheat substitutes are specifically manufactured for patients with celiac disease. Gluten is a protein with limited nutritional value than can be replaced by other dietary proteins. However, the consumption of some nutrients, particularly fibers, iron, calcium, and folate, tends to be lower than normal in patients who adhere to a gluten-free diet. Although no gluten consumption is the ideal treatment for

celiac disease, a minimal degree of gluten contamination is difficult to avoid. The lowest amount of daily gluten that causes damage to the celiac intestinal mucosa over time (the gluten threshold) is 10 to 50 mg per day (a 25-g slice of bread contains approximately 1.6 g of gluten).³⁴ The new Codex Alimentarius³⁵ regulation endorses a maximum gluten contamination of 20 ppm in gluten-free products; this is a safe threshold even for patients who eat large amounts of wheat substitutes. The Food and Drug Administration is in the process of defining safe gluten thresholds.

With maintenance of a gluten-free diet, symptoms and serum celiac antibodies gradually disappear, and healing of the intestinal damage typically occurs within 6 to 24 months after initiation of the diet. However, even when compliance with a gluten-free diet is reported to be good, in a sizable percentage of patients who are symptom-free and have reversion to negative serologic results, minimal intestinal damage persists (most frequently detected as an isolated increase in the intraepithelial lymphocyte count).³⁶ Although considered safe and effective, lifelong elimination of gluten from the diet has psychological and social implications. Adolescents and adults with celiac disease report concerns related to relationships and management of daily life.³⁷ Support and education are important in facilitating patients' adaptation to the new diet.

FOLLOW-UP

Patients should be followed (usually on an annual basis) for life to review adherence to the diet, with serologic monitoring for celiac disease (since persistence or recurrence of abnormal levels of IgA anti-tissue transglutaminase antibodies usually indicates poor dietary compliance) and monitoring for associated conditions (e.g., osteoporosis and autoimmune thyroid disease).

AREAS OF UNCERTAINTY

The role of environmental factors other than gluten in persons who are genetically at risk for celiac disease is currently under scrutiny. Potential modifying factors include breast-feeding (with a reported 50% lower risk among infants who are still being breast-fed when gluten is introduced into the diet than among those who are not),³⁸ the composition of gut microbiota,³⁹ the age at the introduction of gluten into the diet, and the amount

Table 2. Clinical and Pathogenic Differences among Celiac Disease, Gluten Sensitivity, and Wheat Allergy.

Variable	Celiac Disease	Gluten Sensitivity	Wheat Allergy
Interval between exposure to gluten and onset of symptoms	Weeks to years	Hours to days	Minutes to hours
Pathogenesis	Autoimmunity (innate and adaptive immunity)	Possibly innate immunity	Allergic immune response
HLA	Restricted to <i>HLA-DQ2</i> or <i>HLA-DQ8</i> (in approximately 97% of positive cases)	Not restricted to <i>HLA-DQ2</i> or <i>HLA-DQ8</i> (<i>HLA-DQ2</i> -positive, <i>HLA-DQ8</i> -positive, or both in 50% of patients)	Not restricted to <i>HLA-DQ2</i> or <i>HLA-DQ8</i> (<i>HLA-DQ2</i> -positive, <i>HLA-DQ8</i> -positive, or both in 35–40% of patients, similar to the general population)
Autoantibodies	Almost always present	Always absent	Always absent
Enteropathy	Almost always present	Always absent (slight increase in the intraepithelial lymphocyte count)	Always absent (eosinophils in the lamina propria)
Symptoms	Both intestinal and extraintestinal; gastrointestinal symptoms not distinguishable from those of gluten sensitivity and wheat allergy	Both intestinal and extraintestinal; gastrointestinal symptoms not distinguishable from those of celiac disease and wheat allergy	Both intestinal and extraintestinal; gastrointestinal symptoms not distinguishable from those of celiac disease and gluten sensitivity symptoms
Complications	Coexisting conditions; long-term complications	Absence of coexisting conditions and long-term complications	Absence of coexisting conditions; short-term complications (including anaphylaxis)

of gluten consumed. Intestinal infections, particularly rotavirus infection,⁴⁰ have also been suggested as a possible trigger for celiac disease, although this remains controversial.

Despite the high sensitivity and specificity of serologic testing, the diagnosis is not always straightforward, given the possibility of false positive and false negative serologic and biopsy results. The frequency of cases of seronegative celiac disease is likely to be underestimated, since biopsies of the small intestine are mostly performed in patients with positive serologic findings. Serologic tests may have false positive results (usually low antibody titers) in patients with other immune or inflammatory conditions, and the results may be borderline positive in patients with mild enteropathy. The new diagnostic algorithm that has been proposed to avoid intestinal biopsy in children²⁸ requires validation in prospective studies, particularly with respect to the recommended cutoff level of IgA anti-tissue transglutaminase antibodies.

Given the high rate of undiagnosed celiac disease, population-based screening has been proposed, but its benefits and cost-effectiveness are unproved.⁴¹ Case-finding studies — serologic testing in symptomatic or at-risk groups (family members of patients with celiac disease and patients who have conditions known to be associ-

ated with celiac disease) — are currently the standard,⁴² but they do not detect at least 50% of cases diagnosed by means of universal screening.

The assessment of compliance with a gluten-free diet is still unsatisfactory. The persistence of minor intestinal damage at follow-up biopsy^{34,36} in a substantial proportion of persons who report adherence to a strict gluten-free diet and who no longer have antibody titers on serologic testing suggests that occasional dietary lapses are common. The long-term consequences of persistent intestinal damage are unclear.

It is unclear whether oats should also be excluded from a gluten-free diet. The majority of patients with celiac disease can consume a moderate amount of pure oats (up to 70 g per day in adults and 25 g per day in children) without side effects, but side effects do occur in some patients.⁴³

Many people report gluten sensitivity and have a clinical response to a gluten-free diet in the absence of serologic or histologic evidence of celiac disease. However, the frequency, pathophysiology, and natural history of gluten sensitivity, and its relationship to celiac disease, if any, remain to be elucidated. Because of the recent surge of media attention to gluten and its potential adverse effects on health, many people have switched to a gluten-free diet in the absence of medical advice and

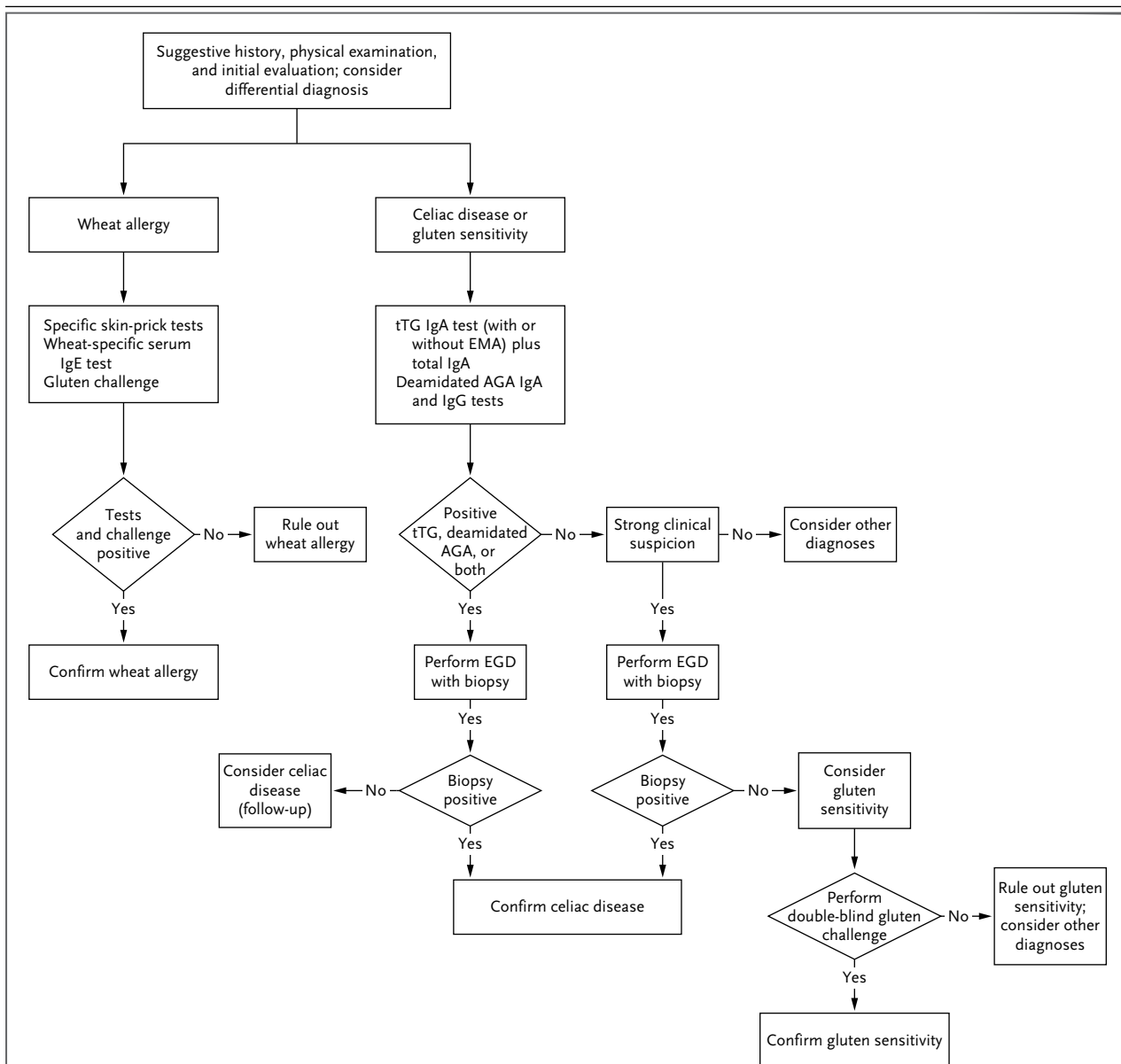


Figure 1. Proposed Algorithm for the Differential Diagnosis of Gluten-Related Disorders.

AGA denotes antigliadin peptide antibodies, EGD esophagogastroduodenoscopy, EMA antiendomysial antibodies, and tTG tissue transglutaminase. Adapted from Sapone et al.⁴⁵

supervision. A reduction in symptoms after the implementation of a gluten-free diet is not pathognomonic of celiac disease, since a placebo effect and other forms of gluten reaction have been described.⁴⁴ Patients with a wheat allergy may also benefit from a gluten-free diet. The distinction among celiac disease, gluten sensitivity, and wheat

allergy can be difficult to establish and should be based on several criteria (Table 2). Since serum biomarkers that are currently available for wheat allergy, like those for celiac disease, are reliable only when patients are exposed to gluten, a diagnostic algorithm (Fig. 1) should be followed while the patient is still consuming gluten.⁴⁵

GUIDELINES

Several professional societies, including the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition,⁴⁶ the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition,²⁸ the American Gastroenterological Association,⁴⁷ and the National Institutes of Health⁴⁸ have published guidelines for the diagnosis and management of celiac disease. Recommendations in the current article are generally concordant with these guidelines.

CONCLUSIONS
AND RECOMMENDATIONS

The patient in the vignette presents with anemia, vitamin D deficiency, and bone loss, raising the

possibility of malabsorption due to celiac disease. Although she does not have characteristic gastrointestinal symptoms (e.g., diarrhea, weight loss, abdominal pain, or a combination of these symptoms), it is appropriate to screen for celiac disease by measuring IgA anti-tissue transglutaminase antibodies, a test that has high sensitivity and specificity. If the results are positive, endoscopy with biopsy of the small intestine is indicated for confirmation, followed by the implementation of a gluten-free diet under the supervision of a knowledgeable dietician.

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- have a governance structure that ensures editorial independence
- have an editor with experience in the position who expects to continue in the position for at least another 3 years
- be financially able to support the editor's participation in ICMJE activities

In considering candidates, the ICMJE may seek to improve the balance of geographic areas and publishing models among its membership.

To apply, editors-in-chief of interested journals should submit the following materials to the ICMJE (at icmje@acponline.org):

- brief curriculum vitae
- cover letter describing the journal, including but not necessarily limited to details of the journal's history, sponsor or publisher, governance structure, publishing model (e.g., subscription, author-pays open access), target audience, print circulation and online traffic, number of manuscript submissions per year, processes used to select material for publication, acceptance rate, databases where indexed, website address, and guidelines for authors
- statement on how the journal might benefit from ICMJE membership and how the ICMJE might benefit from the journal's membership (should not exceed 1000 words)

The deadline for applications is January 31, 2013.